## REMARKS

The presently claimed invention features methods for identifying compounds that are candidate modulators of the drug resistance of an eukaryotic cell. The presently claimed methods entail screening test compounds to identify those compounds that alter the expression of a gene encoding a polypeptide comprising the amino acid sequence encoded by SEQ ID NO:1, a gene whose expression is higher in an EMT-6 derived tumor selected for drug resistance than in an EMT-6 derived tumor that has not been selected for drug resistance.

Because SEQ ID NO:1 is a cDNA sequence rather than a genomic sequence, Applicant has amended claim 23 to refer to a gene "encoding a polypeptide comprising the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:1" rather than a gene "comprising SEQ ID NO:1". No new matter has been added by this amendment.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected claims 23-27 under 35 U.S.C. §112, first paragraph as allegedly not enabled. The Examiner cited two reasons for concluding that the claims are not enabled.

First, the Examiner argued that the claims are not enabled because, according to the Examiner, there are "no teachings in the specification nor any art of record which identify a disease or condition which would benefit from the upregulation of SEQ ID NO:1."

Second, the Examiner argued that the claims are not enabled because, according to the Examiner, the specification "does not disclose or suggest any ... compounds beyond nucleic acids and the proteins encoded thereby for the modulation of the resistance gene" and because the specification does not enable one to use nucleic acids in antisense therapy or gene therapy.

As explained in greater detail below, Applicant disagree with the Examiner's conclusions and maintain that the present claims are enabled.

**The specification discloses at least one disease or condition that would benefit from increased expression of the gene**

Contrary to the Examiner's assertion, the specification does disclose at least one "disease or condition" that would "benefit from the upregulation of SEQ ID NO:1". For example, the specification explains that compounds which upregulate a gene that is upregulated in drug-resistant cells are useful for protecting non-neoplastic cells during chemotherapy.

> Also within the invention is a method for increasing drug resistance in a cell by altering the level of expression of a resistance sequence by administering a compound that alters the expression of the resistance sequence. For example, drug resistance may be increased by increasing the expression of an up-regulated sequence in the cell. Decreasing expression of a down-regulated sequence can increase drug resistance. Such methods are useful for the protection of non-neoplastic cells during chemotherapy (specification at page 8, line 33 – page 9, line 2).

Thus, it is clear that the specification discloses at least one disease or condition that would benefit from increased expression of a gene that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:1. The Examiner does not dispute that the specification discloses uses for compounds that decrease the expression of a gene that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:1. For example, the specification teaches that compounds that decrease expression of a gene that is upregulated in a drug resistant cancer are useful for improving the effectiveness of a chemotherapeutic compound in the treatment of a drug resistant neoplastic disorder, e.g., a cancer (specification at page 5, lines 12-17). The Examiner has explicitly acknowledged that the specification discloses uses for compounds that decrease expression of the gene. Thus, contrary to the Examiner's assertion, the present specification teaches uses for both those compounds that increase expression of the gene and those compounds that decrease expression of the gene.

**The claims are enabled irrespective of whether the specification discloses a disease or condition which would benefit from increased expression of the gene**

The present claims are enabled irrespective of whether the specification discloses a disease or condition that would benefit from increased expression of a gene that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:1. This is because the claims

are drawn to a method that entails determining whether a test compound alters the expression of the gene. In theory, some test compounds will increase expression of the gene, some will decrease expression of the gene, and some will not alter expression of the gene. The claimed screening methods are generically useful for identifying compounds that alter expression of the gene. Thus, both compounds that increase expression of the gene and compounds that decrease expression of the gene can be identified by the claimed methods. The claimed methods are not in some fashion limited to the testing or identification of only those compounds that will increase expression of the gene. Thus, even if the specification only disclosed a use for those test compounds that decrease expression of the gene, the claims are enabled. The situation might be different if the claimed methods could only identify test compounds that increase expression of the gene and if the specification did not disclose a use for such compounds, but that is not the situation here.

**The specification discloses a wide variety of compounds that can be screened to identify candidate modulators of expression**

The Examiner asserted that the only compounds disclosed as potential modulators of expression are nucleic acid molecules and the proteins they encode. The Examiner then went on to argue that the pending claims are not enabled because, according to the Examiner, antisense therapy and gene therapy are not enabled by the present application. The Examiner went on to provide a detailed discussion of some of the challenges associated with antisense therapy and gene therapy. The Examiner's concerns with the challenges associated with antisense therapy and gene therapy are misplaced and undue. Even assuming, without conceding, that antisense therapy and gene therapy and are not predictable and useful, the claims are enabled because there are molecules other than nucleic acids that are disclosed in the specification and that can be screened using the presently claimed methods.

The present claims are not limited to the screening of any particular class of test compound. Thus, as the specification explains, peptides, peptidomimetics, and small molecules are among the test compounds that can be screened using the presently claimed methods.

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, i.e., candidate or test compounds or agents (e.g., peptides, peptidomimetics, small molecules or other drugs) which bind to a resistance protein or have a stimulatory or inhibitory effect on, for example, expression or activity of a resistance sequence. Such identified compounds may be useful for the modulation of drug resistance.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a resistance protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; natural products libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop et al. (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Bio/Techniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (U.S. Patent No. 5,223,409), spores (Patent Nos. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390; Devlin (1990) *Science* 249:404-406; Cwirla et al. (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382; and Felici (1991) *J. Mol. Biol.* 222:301-310) (specification at page 39, line 21 – page 40, line 11).

It is clear that the specification discloses many types of compounds other than nucleic acids that can be screened using the claimed methods. Because the specification enables one skilled in the art to use any type of compound as a test compound in the claimed screening methods, the

present claims are enabled whether or not the specification teaches one how to make and how to use nucleic acid molecules in antisense therapy or gene therapy.

**The claimed subject matter is screening methods, not therapeutic agents or methods**

The Examiner's assertion that antisense therapy and gene therapy are not enabled by the present application is not a valid basis for concluding that the claimed screening methods are not enabled. This is because the claims are drawn to screening methods, not therapeutic agents or therapeutic methods.

The claims are drawn to a "method for determining whether a test compound is a candidate compound for modulating the drug resistance of an eukaryotic cell". Thus, the proper standard for evaluating the enablement and usefulness of the claimed methods is not whether a particular agent that is identified using the claimed method is certain to be useful for modulating drug resistance. Any candidate therapeutic agent identified in an *in vitro* screen will, of course, require considerable further study and testing using other assays and ultimately clinical trials before it can be determined whether it is useful for treating a patient. This is not a reason to conclude that presently claimed screening methods are not enabled. Screening methods that rely on a specific target are valuable because such screening methods can be used to dramatically narrow the group of compounds that are worthy of further study. Moreover, Examiner's position simply ignores the reality of target-based drug discovery. Applicant respectfully points out that the presently claimed methods are but one aspect in the whole of the drug discovery process. Despite the fact that, for various reasons, few compounds identified in target-based screens ultimately prove to be a successful drug, large pharmaceutical companies, small start-up companies, and government and academic researchers the world over spend countless hours and many, many millions of dollars using target-based screens to identify candidate drugs. Those carrying out drug development are well aware of the difficulty of developing a safe and effective therapeutic agent. However, they continue to use target-based screening because they believe that such screens are useful for identifying candidate therapeutic agents. The Examiner cannot

simply dismiss a scientific approach that is so widely used simply because the ultimate goal of the whole of the therapeutic discovery process is difficult to achieve.

## CONCLUSION

The specification provides the teachings needed to allow one skilled in the art to make and to use the invention. The teachings provided include materials and analytical tools for practicing the claimed screening method. Thus, the present claims are enabled. The enablement rejection made by the Examiner is based solely on speculation that certain candidate modulators identified using the methods of the invention will not prove to be effective therapeutic agents. This is not a proper basis for concluding that the present screening claims are not enabled.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §112, first paragraph be withdrawn. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906